



General

Guideline Title

Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline.

Bibliographic Source(s)

Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, Sperduto PW, Vogelbaum MA, Radawski JD, Wang JZ, Gillin MT, Mohideen N, Hahn CA, Chang EL. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol*. 2012 Jul;2(3):210-25. [88 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The U.S. Preventative Services Task Force Levels of Evidence (I-III) are defined at the end of the "Major Recommendations" field.

1. What prognostic factors are important for assessing and managing patients with newly diagnosed brain metastases?

Interpretative Summary

Several prognostic indices have been reported in the literature for survival duration among patients with newly diagnosed brain metastases. These are useful in categorizing patients into survival time strata for treatment decisions, for predicting the results of therapeutic interventions, and for comparing treatment results.

The Radiation Therapy Oncology Group (RTOG) devised three prognostic groups using recursive partitioning analysis based on 1,200 patients treated on prospective clinical trials with whole brain radiotherapy (WBRT) alone or additionally with radiosensitizers: class I, patients with Karnofsky performance status (KPS) ≥ 70 years, less than 65 years of age with controlled primary (3-month stability on imaging or newly diagnosed), and no extracranial metastases; class III, KPS < 70 ; class II, All others. Median survival was 7.1 months, 4.2 months, and 2.3 months for class I, II, and III, respectively.

Brain metastases are a heterogeneous population. The purpose of the graded prognostic assessment (GPA) was to identify significant diagnosis-specific prognostic factors in an updated era (1985-2007) as compared with the RTOG recursive partitioning analysis (RPA) (1979-1993). The original GPA was based on four criteria: age, KPS, number of brain metastases, and presence or absence of extracranial metastases. Each of the four criteria is given a score of 0, 0.5, or 1.0 and these four scores are summed to determine the GPA score. Patients with the best prognosis have a GPA score of 4.0. The authors established this prognostic index based on 1,960 patients treated

with WBRT alone, WBRT and radiosensitizers, or WBRT and radiosurgery in the RTOG database, with all patients and data coming from prospective clinical trials.

The GPA was then refined based on a multi-institutional analysis of 4,259 other patients with brain metastases treated with surgery, WBRT, radiosurgery, or various treatment combinations. New diagnosis-specific prognostic indices (diagnosis-specific graded prognostic assessment) were defined based only on the statistically significant prognostic factors for each individual diagnosis. A subsequent analysis of 400 breast cancer patients refined the breast-GPA scoring system.

Table 3 in the original guideline document shows the GPA scoring criteria for each of the significant prognostic factors by diagnosis. Table 4 in the original guideline document shows the associated range of median survival by GPA and diagnosis.

Other prognostic indices such as the score index for radiosurgery, the basic score for brain metastases, the Golden grading system, and the Rades prognostic scoring system have also been published.

Newly Diagnosed Brain Metastases: Single Brain Metastasis, Role for Surgery

2. For patients with single brain metastasis (excluding radiosensitive histologies such as small cell lung cancer, leukemia, lymphoma, and germ cell tumor), does surgical resection and whole brain radiotherapy improve survival or brain control compared with whole brain radiotherapy alone or compared with surgical resection alone?

Interpretative Summary

For selected patients with good performance status (e.g., KPS ≥ 70), limited extracranial disease, and a resectable brain metastasis, complete resection of the single brain metastasis improves the probability of extended survival. The addition of postoperative whole brain radiotherapy improves treated brain metastasis control and overall brain control without improving overall survival or duration of functional independence. These interpretations are consistent with the American Association of Neurological Surgeons (AANS) guidelines on the use of surgery.

Newly Diagnosed Brain Metastases: Single Brain Metastasis, Surgery Versus Radiosurgery

3. Is survival or brain control different in selected patients with single brain metastasis (excluding radiosensitive histologies such as small cell lung cancer, leukemia, lymphoma, and germ cell tumor) treated with surgery or radiosurgery?

Interpretative Summary

There have been no high quality randomized trials that have assessed whether selected patients with a small single brain metastasis, in surgically accessible sites, should undergo radiosurgery or resection. Adding WBRT did not improve overall survival or functional independence.

Newly Diagnosed Brain Metastases: Single or Multiple Brain Metastasis(es), WBRT with or without Radiosurgery Boost

4. Is there a survival or brain control difference in patients treated with WBRT and radiosurgery boost versus WBRT alone?

Interpretative Summary

For good prognosis patients with single brain metastases (less than 4 cm in size, in patients with good performance status and controlled extracranial disease), the use of radiosurgery added to WBRT improves survival, treated brain lesion control, and overall brain control as compared with WBRT alone.

In good prognosis patients with multiple brain metastases (all less than 4 cm in size and up to four brain metastases in number), radiosurgery boost when added to WBRT improves treated brain lesion and overall brain control as compared with WBRT alone. As there is no survival advantage with radiosurgery added to WBRT in patients with multiple brain metastases, WBRT alone may be considered.

One randomized trial (RTOG 9508) that included patients with up to three brain metastases found an improvement in KPS and decreased steroid use at 6 months with the use of radiosurgery boost added to WBRT. These interpretations are consistent with the AANS guidelines on the use of radiosurgery boost.

Newly Diagnosed Brain Metastases: Single or Multiple Brain Metastasis(es), Radiosurgery Alone Versus WBRT and Radiosurgery

5. Is there survival, brain control difference, or neurocognitive difference in patients treated with radiosurgery alone versus WBRT and radiosurgery?

Interpretative Summary

Selected patients with brain metastasis(es) may be treated with radiosurgery alone. A further alternative is WBRT and radiosurgery boost. A third option for selected patients with multiple brain metastases is WBRT alone. There have been no convincing survival differences among the three options listed above, although none of the trials have been adequately powered to detect anything other than very large survival differences.

More trials are needed to assess whether there are differences in neurocognitive and quality of life outcomes when WBRT is omitted in selected patients who are treated with radiosurgery alone.

Newly Diagnosed Brain Metastases: Multiple Brain Metastases

6. What is the role of comfort measures or palliative supportive care alone versus WBRT in patients with multiple brain metastases?

Interpretative Summary

For selected patients with poor life expectancy (less than 3 months), the use of whole brain radiotherapy may or may not significantly improve symptoms from brain metastases. Comfort measures only, or short course (20 Gy in five daily fractions) whole brain radiotherapy, are reasonable options.

7. What is the optimal WBRT dose fractionation schedule?

Interpretative Summary

No differences in overall survival or symptom control have been demonstrated among the commonly used fractionation schemes, including 30 Gy in 10 daily fractions or 20 Gy in five daily fractions. Other common dose fractionation schedules of WBRT are 37.5 Gy in 15 daily fractions and 40 Gy in 20 daily (or twice daily) fractions. This interpretation is consistent with the AANS guideline on whole brain radiotherapy.

8. What is the role of WBRT and radiosensitizers versus WBRT alone in the management of patients with brain metastases?

Interpretative Summary

There is no evidence of survival benefit with the use of radiosensitizers and whole brain radiotherapy.

9. What is the role of chemotherapy and WBRT?

Interpretative Summary

Although chemotherapy trials reported improved brain response rates with the use of combined chemotherapy and WBRT, this was at the cost of toxicity and no overall survival advantage was found with the addition of chemotherapy. There currently is no high quality evidence to support the routine use of chemotherapy in the management of brain metastases.

Definitions:

U.S. Preventative Services Task Force Levels of Evidence

Level I: Evidence obtained from at least one properly designed randomized controlled trial

Level II-1: Evidence obtained from well-designed controlled trials without randomization

Level II-2: Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than one center or research group

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results from uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Newly diagnosed brain metastasis(es)

Guideline Category

Management

Treatment

Clinical Specialty

Neurological Surgery

Neurology

Oncology

Radiation Oncology

Radiology

Surgery

Intended Users

Patients

Physicians

Guideline Objective(s)

To systematically review the evidence for the radiotherapeutic and surgical management of patients newly diagnosed with intraparenchymal brain metastases

Target Population

Patients with newly diagnosed brain metastasis(es)

Interventions and Practices Considered

1. Surgical resection
2. Whole brain radiotherapy (WBRT)
3. Radiosurgery
4. Palliative supportive care
5. Radiosensitizers
6. Chemotherapy

Major Outcomes Considered

- Prognostic value of assessments
- Survival

- Brain control
- Neurocognitive function
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

MEDLINE (1966-Nov. 3, 2010), EMBASE (1980-2010 week 46), and the CENTRAL databases (issue 4, 2010) were searched (see Appendix 1 in the original guideline document). The search strategies resulted in 1,826 publications, 597 publications, and 425 publications from MEDLINE, EMBASE, and CENTRAL, respectively (search strategy courtesy of the Cochrane Library). Only randomized phase III trials pertinent to the management of newly diagnosed brain metastases were included. Trials dealing with the use of whole brain radiotherapy (WBRT), surgery, radiosurgery, chemotherapy, radiosensitizers, and palliative care alone were considered. Trials that examined the use of prophylactic cranial irradiation were excluded. A total of 36 randomized controlled trials were retrieved (see the "Rating Scheme for the Strength of Evidence" field). One trial was excluded as it was published in abstract form in the year 2000 but never fully reported. Two duplicate publications of the same trial were included.

As a result of feedback received from public comments, the literature search was further expanded to include nonrandomized studies (prospective or retrospective) dealing with the use of either radiosurgery or fractionated radiation to the postoperative surgical cavity. The MEDLINE (1947 to May week 2, 2011) search resulted in 1,549 nonrandomized publications and EMBASE (1980-2011 week 20) gave 3,721 nonrandomized publications. The CENTRAL search resulted in zero randomized controlled trials. Titles and abstracts were screened and a final total of 15 relevant publications were retrieved.

Of note, all the radiosurgery trials used frame-based single fraction radiosurgery techniques with either a linear accelerator or gamma knife unit.

Number of Source Documents

A total of 36 randomized controlled trials were retrieved from the first literature search. A total of 15 relevant publications were retrieved from the second literature search.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

U.S. Preventative Services Task Force Levels of Evidence

Level I: Evidence obtained from at least one properly designed randomized controlled trial

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Level II-2: Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than one center or research group

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results from uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Lead representatives from international radiation oncology groups, the American Society for Radiation Oncology (ASTRO), Canadian Association of Radiation Oncology (CARO), European Society for Therapeutic Radiology and Oncology (ESTRO), and Trans-Tasman Radiation Oncology Group (TROG), reviewed the retrieved trials.

Management options were graded by the level of evidence available using the U.S. Preventative Services Task Force levels. Due to the lack of high-quality studies, management of patients with recurrent metastatic disease to the brain is not included in this report.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This Guideline builds on the previous American Society for Therapeutic Radiology and Oncology (ASTRO) Health Services Research Committee publication "The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases."

The Task Group was composed of recognized experts in the fields of radiotherapy, surgery, and radiosurgery for brain metastases. These experts represent radiation oncology, neurosurgery, physics, outcomes, and health services research. The Task Group was asked to systematically review the literature on the radiotherapeutic and surgical management for patients with newly diagnosed metastatic disease to the brain. In January 2010, the ASTRO Board of Directors authorized the Task Group membership. The Task Group participated in a series of communications by e-mail and conference calls to review the relevant publications, to discuss controversial issues, and formulate the Guidelines. The Task Group agreed by consensus on the various recommendations based on the randomized trials and relevant publications.

This document was prepared by the Guidelines Subcommittee of the Clinical Affairs and Quality Committee (CAQC) of ASTRO in coordination with the Third International Consensus Conference on Palliative Radiotherapy.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The initial draft of the manuscript was reviewed by three expert reviewers and was placed on the American Society for Radiation Oncology (ASTRO) website during the month of April 2011 for public comment. Upon integration of the feedback, the document was then submitted to the ASTRO Board of Directors for their final review and approval in October 2011.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is not specifically stated for each recommendation.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate radiotherapeutic and surgical management for patients with newly diagnosed brain metastasis(es)

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- Adherence to this Guideline will not ensure successful treatment in every situation. Furthermore, this Guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all circumstances presented by the individual patient. The American Society for Radiation Oncology assumes no liability for the information, conclusions, and findings contained in its Guidelines.
- This Guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jul

Guideline Developer(s)

American Society for Radiation Oncology - Professional Association

Source(s) of Funding

American Society for Radiation Oncology

Guideline Committee

Guidelines Subcommittee of the Clinical Affairs and Quality Committee (CAQC) Task Force

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Financial Disclosures/Conflicts of Interest

Conflicts of interest: Before initiation of this Guideline, all members of the Guidelines Task Group were required to complete disclosure statements. These statements are maintained at the American Society for Radiation Oncology (ASTRO) headquarters in Fairfax, Virginia and pertinent disclosures are published with the report. The ASTRO Conflict of Interest Disclosure Statement seeks to provide a broad disclosure of outside interests. Where a potential conflict is detected, remedial measures to address any potential conflict are taken and will be noted in the disclosure statement.

Dirk Rades has received research grants from Merck Serono and Novartis, and serves as a consultant for Amgen and Astra Zeneca. Michael Vogelbaum has received research funding from Schering-Plough, Genentech, Brainlab, and Astra Zeneca; he owns stock in Johnson and Johnson. Jian Wang has received a prostate cancer research grant from the Ohio Cancer Research Associates. Expert reviewers were also required to complete disclosure statements, which are maintained at ASTRO Headquarters. The Task Group Chairs reviewed all disclosures and determined that they were not relevant to the subject matter of the Guideline.

Guideline Endorser(s)

Congress of Neurological Surgeons - Professional Association

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [Practical Radiation Oncology Web site](#) .

Availability of Companion Documents

The following is available:

- Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. CME course. Available from the [American Society for Radiation Oncology Web site](#) .

Patient Resources

The following is available:

- Radiation therapy for brain metastases. Brochure. Fairfax (VA): American Society for Radiation Oncology; 2012. 2 p. Electronic copies: Available from the [RT Answers Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide

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NGC Status

This NGC summary was completed by ECRI Institute on July 24, 2012. The information was verified by the guideline developer on August 22, 2012.

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